AF/1631
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Rev 01/30/04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Thomas C. Terwilliger	Docket No.:	S-96,583
Serial No.:	10/017,643	Examiner:	Marschel
Filed :	12/12/2001	Art Unit:	1631

For : METHOD FOR REMOVING ATOMIC-MODEL BIAS IN MACROMOLECULAR CRYSTALLOGRAPHY

Mail Stop Appeal Brief - Patents
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL OF APPEAL BRIEF

1. Transmitted herewith in triplicate is the Appeal Brief in this application with respect to the Notice of Appeal filed on May 18, 2004.

2. ☐ Applicant claims small entity status.

3. Attached is a Fee Transmittal Form.

Respectfully submitted,

Date: June 2, 2004

Signature of Attorney

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CERTIFICATE OF MAILING/TRANSMISSION (37 CFR 1.8(a))

I hereby certify that this correspondence is, on the date shown below, being:

MAILING

☒ deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

Date: June 2, 2004

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Signature

Ray G. Wilson
(type or print name of person certifying)

Rev. 03/05/04

FEE TRANSMITTAL
For FY 2004

Patent fees are subject to annual revision

☐ Applicant claims small entity status. See 37 CFR 1.27

TOTAL AMOUNT OF PAYMENT: $330.00

Complete if Known	
Application Number:	10/017,643
Filing Date:	12/12/2001
First Named Inventor:	Thomas C. Terwilliger
Examiner Name:	Marschel
Group/Art Unit:	1631
Attorney Docket No.:	S-96,583

METHOD OF PAYMENT (check all that apply)

1. ☒ The commissioner is hereby authorized to charge indicated fees and credit any over payments to:
   Deposit Account Number: **12-2150**
   Deposit Account Name: **Los Alamos National Laboratory**
   ☒ Charge Any Additional Fee Required Under 37 C.F.R. 1.16 and 1.17

FEE CALCULATION

1. BASIC FILING FEE

Large Entity Fee		Small Entity Fee		Fee Description	Fee Paid
1001	$770	2001	$385	Utility filing fee	
1004	$770	2004	$385	Reissue filing fee	
1005	$160	2005	$80	Provisional filing fee	

SUBTOTAL (1) $000.00

2. EXTRA CLAIM FEES

		Extra Claims	Fee from Fee Paid Below
Total Claims	–20** =	X	=
Independent Claims	–3 ** =	X	=
Multiple Dependent			=

*** or number previously paid, if greater; For Reissues, see below*

Large Entity Fee		Small Entity Fee		Fee Description
1202	$18	2202	$9	Claims in excess of 20
1201	$86	2201	$43	Independent claims in excess of 3
1203	$290	2203	$145	Multiple dependent claim, if not paid.
1204	$86	2204	$43	** Reissue independent claims over original patent
1205	$18	2205	$9	** Reissue claims in excess of 20 and over original patent

SUBTOTAL (2) $

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Large Entity Fee Code	Fee ($)	Small Entity Fee Code	Fee ($)	Fee Description	Fee Paid
1051	**$130**	2051	**$65**	Surcharge – late filing fee or oath	
1052	**$50**	2052	**$25**	Surcharge – late provisional filing fee or cover sheet	
1812	**$2,520**	1812	**$2,520**	For filing a request for reexamination	
1251	**$110**	2251	**$55**	Extension for reply within first month	
1252	**$420**	2252	**$210**	Extension for reply within second month	
1253	**$950**	2253	**$475**	Extension for reply within third month	
1254	**$1,480**	2254	**$740**	Extension for reply within fourth month	
1255	**$2,010**	2255	**$1,005**	Extension for reply within fifth month	
1401	**$330**	2401	**$165**	Notice of Appeal	
1402	**$330**	2402	**$165**	Filing a brief in support of an appeal	**$330.00**
1403	**$290**	2403	**$145**	Request for oral hearing	
1452	**$110**	2452	**$55**	Petition to revive – unavoidable	
1814	**$110**	2814	**$55**	Terminal Disclaimer	
1453	**$1,330**	2453	**$665**	Petition to revive – unintentional	
1460	**$130**	1460	**$130**	Petitions to the Commissioner	
1806	**$180**	1806	**$180**	Submission of Information Disclosure Statement	
1809	**$770**	2809	**$385**	Filing a submission after final rejection (37 CFR 1.129 (a))	
1810	**$770**	2810	**$385**	For each additional invention to be examined (37 CFR 1.129(b))	
1811	**$100**	1811	**$100**	Certificate of Correction	
1504	**$300**	1504	**$300**	Publication fee for early, voluntary, or normal publication	
1801	**$770**	2801	**$385**	Request for Continued Examination (RCE)	

Other fee (specify) _____

SUBTOTAL (3) $

Reduced by Basic Filing Fee Paid

SUBTOTAL FROM 1 $
SUBTOTAL FROM 2 $
SUBTOTAL FROM 3 $330.00

TOTAL AMOUNT OF PAYMENT $330.00

SUBMITTED BY			Complete (if applicable)	
Printed Name:	Ray G. Wilson		Reg. No.	28,351
Signature:	Ray G. Wilson	Date: 06/02/04	Telephone	(505) 665-3112

01/30/04

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Appellants:	Thomas C. Terwilliger	Docket No.:	S-96,583
Serial No.:	10/017,643	Examiner:	Marschel
Filed :	December 12, 2001	Art Unit:	1631
For :	METHOD FOR REMOVING ATOMIC-MODEL BIAS IN MACROMOLECULAR CRYSTALLOGRAPHY		

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APPEAL BRIEF

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
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STATEMENT OF THE REAL PARTY IN INTEREST

The Regents of the University of California is the assignee of all right, title, and interest in U.S. Patent Application Serial No. 10/017,643 from the Government of the United States, United States Department of Energy.

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences related to this case.

STATUS OF ALL CLAIMS

This is an appeal from the final rejection (Examiner's Action dated February 24, 2004) of Claims 1-8 currently pending in the subject patent application. No claims have been allowed.

STATUS OF AMENDMENTS

No amendments have been filed subsequent to this appeal.

SUMMARY OF THE INVENTION

Structure factor bias in an electron density map for an unknown crystallographic structure is minimized by using information in a first electron density map to elicit expected structure factor information. (Page 11, lines 20-32; Page 12, lines 1-14) Observed structure factor amplitudes are combined with a starting set of crystallographic phases to form a first set of structure factors. (Page 7, lines 5-8) A first electron density map is then derived and features of the first electron density map are identified to obtain expected distributions of electron density. (Page 7, lines 10-16) Crystallographic phase probability distributions are established for possible crystallographic phases of reflection *k,* and the process is repeated as *k* is indexed through all of the plurality of reflections. (Page 7, lines 16-28) An updated electron density map is derived from the crystallographic phase probability distributions for each one of the reflections. (Page 8, lines 10-16) The entire process is then iterated to obtain a final set of crystallographic phases with minimum bias from known electron density maps. (Page 8, lines 14-15)

ISSUE PRESENTED FOR REVIEW

1. Whether Claims 1-8 were properly rejected under 35 U.S.C. §101 as directed to non-statutory matter.
2. Whether Claims 1-8 were properly rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which appellant regards as the invention.
3. Whether Claims 1-5 and 8 were properly rejected under 35 U.S.C. §101(b) and (e)(2) as anticipated by U.S. Patent 5,353,236 to Subbiah.

GROUPING OF THE CLAIMS

Appellants do not believe that any special grouping of the claims leads to a better understanding of the issues.

ARGUMENT

Appellant respectfully traverses the rejection of the claims under 35 U.S.C. §101 as directed to non-statutory subject matter. The Examiner has rejected Claims 1-4 under 35 U.S.C. §101, remarking that the claimed process is directed to non-statutory subject matter since the process manipulates electron density data "without resulting in any physical transformation outside of a computer or other computational device." As noted in MPEP 2106.IV.B.2.(b).(i), a process is clearly statutory "if it requires physical acts to be performed outside the computer . . . . But, "[i]f a claim does not clearly fall into one or both of the safe harbors, the claim may still be statutory if it is limited to a practical application in the technological arts." The next section of MPEP provides an example: " . . .a computer process that simply calculates a mathematical algorithm that models noise is nonstatutory. However, a claimed process for digitally filtering noise employing a mathematical algorithm is statutory."

> The notion of "physical transformation" can be misunderstood. In the first place, it is not an invariable requirement, but merely one example of how a mathematical algorithm may bring about a useful application.
> ***AT&T Corp. v. Excel Communications, Inc.***, 172 F.3d 1352, 50 USPQ 2d 1447, 1454 (Fed. Cir. 1999), *cert denied*, 120 S. Ct. 368 (1999), *on remand*, 52 USPQ2d 1865 (D. Del. 1999)

> Today, we hold that the transformation of data, representing discrete dollar amounts, by a machine through a series of mathematical calculations into a final share price, constitutes a practical application of a mathematical algorithm, formula, or calculation, because it produces "a useful, concrete and tangible result"--a final share price momentarily fixed for recording and reporting purposes and even accepted and relied upon by regulatory authorities and in subsequent trades.
> ***State Street Bank & Trust Co. v. Signature Fin. Group, Inc.***, 47 USPQ 2d 1596, 1601 (Fed. Cir.), ***cert. denied***, 525 U.S. 1093 (1999)

> It is clear from the written description of the . . . patent that AT&T is only claiming a process that uses the Boolean principle in order to determine the value of the PIC indicator. The PIC indicator represents information about the call recipient's PIC, a useful, non-abstract result that facilitates differential billing of long-distance calls made by an IXC's subscriber. Because the claimed process applies the Boolean principle to produce a use, concrete, tangible result without pre-empting other uses of the mathematical principle on its face the claims process comfortably falls within the scope of Section 101. *See Arrhythimia Research Tech. Inc. v. Corazonix Corp.*, 958 R.2d 1053, 1060, 22 USPQ2d 1033, 1039 (Fed. Cir. 1992) ('That the product is numerical is not a criterion of whether the claim is directed to statutory subject.') *Id.*.
> ***AT&T Corp. v. Excel Communications, Inc.***, *supra.* at 1452.

Appellant's claimed method is the application of mathematical algorithms to modify "an electron density map of an experimental crystal structure," resulting in a new electron density map, as recited in Claim 10. There is no longer in the law any requirement that the method result in any "physical transformation" as would be required by the Examiner. Further, the application of the recited mathematical manipulations is clearly directed a specified application, the formation of a revised electron density map of a crystal structure from a starting electron density map. There is no attempt to claim or forestall the use of any mathematical manipulation in any other application. See, e.g., the following claim steps:

(a) obtaining by x-ray diffraction observed structure factor amplitudes for a plurality of reflection from the crystal structure;

(b) selecting a starting set of crystallographic phases . . .;

(d) identifying features of the first electron density map . . .;

(e) making a comparison between the first electron density map and the expected distribution of electron density;

(g) establishing crystallographic phase probability distributions from the comparisons . . .;

(i) deriving an updated electron density map using crystallographic phases determined to be most probable . . . .

Independent Claims 1-8 clearly produce a concrete, tangible result within the teachings of AT&T Corp., *supra.,* and State Street Bank & Trust Co., supra. Even assuming that the electron density map is "the formation of data based on a crystal

structure," as characterized by the Examiner, this is not a criteria for determining whether the claims are directed to statutory subject matter.

Appellant respectfully traverses the rejection of Claims 1-8 under 35 U.S.C. §112, second paragraph, as being indefinite for reciting "a plurality of reflections." No specific number of reflections are claimed or taught in appellant's specification since persons of ordinary skill in the art select some number of reflections depending on a desired resolution, as illustrated in Subbiah at Col. 8, lines 1-9.

The Examiner does not question the use of the term "plurality" and comments that "A plurality of reflections is reasonably interpreted as being as few as two."

> In rejecting a claim under the second paragraph of 35 USC 112, it is incumbent on the examiner to establish that one of ordinary skill in the pertinent art, when reading the claims in light of the supporting specification, would not have been able to ascertain with a reasonable degree of precision and particularity the particular area set out and circumscribed by the claims.
> **Ex parte Wu**, 10 USPQ2d 2031, 2033 (B.P.A.I. 1989)

> An applicant is entitled to claims as broad as the prior art and his disclosure will allow.
> **In re Rasmussen**, 211 USPQ 323, 326 (C.C.P.A. 1981)

Appellant has distinctly claimed a plurality of reflections since at least two reflections are required to perform the process claimed by appellant. However, there is no upper limit on the number of reflections that might be used. Indeed, an electron density map can be constructed from a single reflection (see, e.g., Subbiah at Col. 4, lines 29-32) so that the claimed process could be practiced with as few as two reflections. The exact number of reflections will simply be determined to a resolution determined by the experimenter. Appellant's process provides a modified first electron density map by recognizing features in an initial map that yield expected electron density distributions, which are used to obtain crystallographic phase probability distributions. This is done for all of the plurality (at least two) of reflections, where the most probable crystallographic phases are selected from the resulting maps to provide an updated electron density map. No undue experimentation is required for this determination since a large number of reflections are conventionally recorded, as illustrated by Subbiah.

The rejection of Claims 1-8 under 35 U.S.C. §112, second paragraph, should not be sustained.

Finally, appellant respectfully traverses the rejections of Claims 1-5 and 8 under 35 U.S.C. §102(b) and (e)(2) as being clearly anticipated by U.S. Patent 5,353,236 to Subbiah. Subbiah begins with measured amplitudes of structure factors, but no phase information, and yields phases and an electron density map. See, e.g., Col. 4, lines 27-35:

> The process is started with a low-resolution envelope of the macromolecular crystal. That envelope is used to obtain the phrase of the structure factor for one (or a few) low-resolution reflections. The phase of that structure factor is then used to construct a new, higher resolution envelope which is, in turn, used to calculate the phase for a higher resolution reflection so that an even higher resolution envelope can be constructed.

In another aspect, Subbiah finds arrangements of atomic scatterers that lead to calculated amplitudes of structure factors that are maximally consistent with measured amplitudes of structure factors.

In contrast, the claimed process of the present invention begins with measured amplitudes of structure factors and a set of starting phases are selected, not calculated from an envelope, and yields estimates of phases and an electron density map that have reduced bias. The input phases are adjusted to yield a map that has characteristics anticipated from the map features, but that were not used in constructing the initial estimates of phases. Appendix B presents a comparison of appellant's claim limitations with the Examiner's remarks and the corresponding teachings of Subbiah to the extent appellant could determine which claim limitation was covered by a reference to Subbiah.

To anticipate appellant's claimed invention, Subbiah must disclose every limitation in appellant's claimed process.

> We think the precise language of 35 U.S.C 102 that "a person shall be entitled to a patent unless," concerning novelty and unobviousness, clearly places a burden of proof on the Patent Office which requires it to produce the factual basis for its rejection of an application under sections 102 and 103 . . . .
> **In re Warner**, 154 USPQ 173, 177 (C.C.P.A. 1967, **cert. denied**, 389 U.S. 1057 (1968).

> An anticipating reference must describe the patented subject matter with sufficient clarity and detail to establish that the subject matter existed and that its existence was recognized by persons of ordinary skill in the field of the invention. **ATD Corp. v. Lyndall, Inc.**, 48 USPQ2d 1321, 1328 (Fed. Cir. 1998).

Referring to Appendix B, it is clear that Subbiah fails to disclose at least the following claimed process steps:

(b) selecting a starting set of crystallographic phases to combine with the observed structure factor amplitudes to form a first set of structure factors;

(d) identifying features of the first electron density map to obtain expected distributions of electron density;

(e) making a comparison between the first electron density map and the expected distribution of electron density;

(f) estimating how changes in the crystallographic phase of a reflection *k* affect the comparison;

(g) establishing crystallographic phase probability distributions from the comparisons for the possible crystallographic phases of reflection *k*;

(h) repeating steps (c) through (g) as *k* is indexed through all of the plurality of reflections;

(i) deriving an updated electron density map using crystallographic phases determined to be most probable from the crystallographic phase probability distributions for each one of the reflections;

(j) repeating steps (d) through (i) to obtain a final set of crystallographic phases with minimum bias from known electron density maps.

Subbiah, Col. 10, line 48, through Col. 21, line 38, referenced by the Examiner to show details of the Subbiah improvement process, teaches only moving scatterers about the map grid, calculating the Fourier amplitudes as the scatterers are moved, and correlating the calculated amplitudes with experimental X-ray diffraction data. A person skilled in the art would not possibly recognize Subbiah as having any teaching about establishing comparisons by altering crystallographic phases to establish crystallographic phase probability distributions.

The rejection of Claims 1-8 under 35 U.S.C. §102(b) and (e)(2) should not be sustained.

CONCLUSION

Appellants believe that the Examiner has not made a *prima facie* case for the rejections of currently pending Claims 1-8 under 35 U.S.C. §101, 35 U.S.C. §112, second paragraph, or 35 U.S.C. §102(b) and (e)(2). Appellants have definitely described and claimed a statutory process that is not taught by Subbiah. The rejection of Claims 1-8 should be reversed and this case passed to issue.

Respectfully submitted,

Date: June 1, 2004

Signature of Attorney

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APPENDIX A - CLAIMS ON APPEAL

1. A method for improving an electron density map representing a crystal structure comprising:

(a) obtaining by x-ray diffraction observed structure factor amplitudes for a plurality of reflections from the crystal structure;

(b) selecting a starting set of crystallographic phases to combine with the observed structure factor amplitudes to form a first set of structure factors;

(c) deriving a first electron density map from the first set of structure factors;

(d) identifying features of the first electron density map to obtain expected distributions of electron density;

(e) making a comparison between the first electron density map and the expected distribution of electron density;

(f) estimating how changes in the crystallographic phase of a reflection *k* affect the comparison;

(g) establishing crystallographic phase probability distributions from the comparisons for the possible crystallographic phases of reflection *k*;

(h) repeating steps (c) through (g) as *k* is indexed through all of the plurality of reflections;

(i) deriving an updated electron density map using crystallographic phases determined to be most probable from the crystallographic phase probability distributions for each one of the reflections;

(j) repeating steps (d) through (i) to obtain a final set of crystallographic phases with minimum bias from known electron density maps; and

(k) forming a final electron density map using the final set of crystallographic phases.

2. The method of Claim 1, wherein identifying features of the electron density map includes making probability estimates of whether each point in the map is located in a solvent region or a crystal structure region.

3. The method of Claim 1, wherein identifying features of the election density map includes estimates of whether the electron density at each point in the map is

related by non-crystallographic symmetry to electron density at another point in the map.

4. The method of Claim 1, includes estimates of whether a structural motif is located at each point in the map.

5. The method of Claim 4, wherein the structural motif is a helix.

6. The method of any one of Claims 1, 2, 3, or 4, wherein the crystallographic phase probability distributions are log-likelihood functions.

7. The method of Claim 1, further including the steps of calculating first and second derivatives for the crystallographic phase probability distributions with respect to the structure factors; and

applying an FFT-based algorithm to determine the most probable crystallographic phase probability distributions.

8. The method of Claim 1, wherein the step of selecting a starting set of crystallographic phases includes;

selecting a model crystal structure having similarities to the crystal structure being examined;

assigning a low weighting factor to structure factors of the model crystal structure; and

combining the weighted structure factors with the observed structure factors for deriving the first electron density map.

APPENDIX B
CLAIM COMPARISON WITH REJECTION

Claim limitation	Examiner's comment	Reference citation	Appellant's comment
1. A method for improving an electron density map representing a crystal structure comprising:	Subbiah is directed to the crystallographic modeling of macromolecules as cited in the title and abstract with the construction of regions of units cells from diffraction patterns and Fourier amplitudes and to calculate electron density distributions as is also the subject matter of the instant claims.	Abstract: A method for constructing an image of a macromolecular crystal includes steps of providing an envelope which defines the region of a unit cell occupied by the macromolecule; distributing a collection of scattering bodies within the envelope; condensing the collection of scattering bodies to an arrangement that maximized the correlation between the diffraction pattern of the crystal and a pattern of Fourier amplitudes for the collection of scattering bodies; determining the phase associated with at least one of the Fourier amplitudes of the condensed collection of scattering bodies; calculating an electron density distribution of the crystal from the phase information; and defining an	Appellant's invention is directed to providing an improved electron density map of a crystal structure. Subbiah teaches a method for obtaining a high resolution of an envelope of the crystal structure (column 21, lines 23-26).

		image of the macro molecule in the electron density distribution.	
(a) obtaining by x-ray diffraction observed structure factor amplitudes for a plurality of reflections from the crystal structure;	This column 21 citation (column 21, lines 5-16) also discloses the utilization of the reflections in the diffraction pattern as also instantly claimed.	After 100-200 reflections have been used to calculate new envelopes, it will often be desirable to step in larger increments (i.e., more than one reflection will be phased in a given PW ["phase walk"] step). This will expedite the procedure, often without introducing significant new error. In addition, any such new errors are likely to be due to the weaker reflections. Thus, the risk of introducing error at these larger PW steps can be minimized by considering only the stronger reflections. Preferably, the larger PW steps will be done in increments of up to about 15% of the total number reflections phased thus far.	Subbiah does use reflection in a diffraction pattern, as does the present invention, but the initial calculations are used to obtain the phase of the structure factor (column 10, lines 58-61), not structure factor amplitudes.
(b) selecting a starting set of crystallographic phases to combine with the observed structure factor amplitudes to form a first set of structure factors;	In column 4, lines 22-42, the construction of a low resolution envelope for the electron density distribution is disclosed	The present invention produces a high-resolution model of the electron density distribution of a macromolecule in a defined asymmetric unit of a crystal lattice. This is accomplished	In Subbiah, the phases are determined from the reflection data, as stated in the citation. Applicant selects a starting set of crystallographic

		through a simple and rapid method for determining the phases of the reflection data for the macromolecule of interest. The process is started with a low-resolution envelope of the macromolecular crystal. That envelope is used to obtain the phase of the structure factor for one (or a few) low-resolution reflection. The phase of that structure factor is then used to construct a new, higher resolution, envelope which is, in turn, used to calculate the phase so a higher resolution reflection so that an even higher resolution envelope can be constructed. In this manner, the resolution of the envelope is improved by bootstrapping the solution from earlier calculations and the diffraction data. The process can be terminated at any stage, regardless of resolution. Thus, if the desired resolution is only intermediate, the process of this invention can be	phases to combine with observed structure factors amplitudes derived from the reflection data to form a first set of structure factors. This starting set of crystallographic phases is selected from a model or other source (page 5, lines 19-22), not the reflection data.

		terminated after the diffraction data of intermediate resolution has been phased.	
(c) deriving a first electron density map from the first set of structure factors;		Column 11, lines 22-26: If the low-resolution image is provided in the form of an electron density map, it [the image] can be expanded by simply choosing its boundaries to be the region circumscribed by a relatively low electron density contour.	In Subbiah, the electron density map is used only as an image to establish the envelope that is progressively refined by Subbiah. No further use is made of the electron density map.
(d) identifying features of the first electron density map to obtain expected distributions of electron density;	Particular structural motifs as in instant claims 4 and 5 are recognized in the map in the reference as disclosed in column 21, lines 34-39. Solvent regions and corresponding probability estimates are also described in the reference in column 20, lines 36-41, as required in instant claim 2.	For proteins, structural motifs such as inter-domain clefts and other prominent surface indentations, are typically observed at low resolution. At higher resolution, sheets, helices, side chains, and ultimately, atoms may be observed. As an example, the solvent may be expected to occupy 55% of the asymmetric unit volume (and the macro-molecule would occupy the remaining 45%). The scatterers might initially be placed in many more grip elements than would be expected for the	Subbiah uses the high resolution envelope to display features of the macromolecule, as particularly discussed at column 21, lines 23-39. There is no teaching about using the features to obtain any expected distributions of electron density. The example of Subbiah simply expresses a percentage of the cell unit volume occupied by solvent and by macromolecule, not any distribution of electron density.

		macromolecule.	
(e) making a comparison between the first electron density map and the expected distribution of electron density;	It is noted that each envelope of higher resolution is an estimated electron density distribution which is then compared with further phase refinement and reflection calculations to result in such practice as in the instant claims. (No specific citation was provided, so see column, lines 3-12)	After the new electron density map has been prepared, scatterers are placed in regions of high electron density. Typically, the asymmetric unit is divided into a grid of perpendicular lines, defining boxes that can each accommodate a single scatterer. As the resolution increases in succeeding PW steps, the fineness of the grid should also increase to allow for additional scatterers per unit volume. The grid will preferably accommodate three scatterers (and generally in the range of 1 to 6) per one-dimensional unit of the current resolution.	Subbiah makes no comparison between an electron density map and an expected distribution of electron density.
(f) estimating how changes in the crystallographic phase of a reflection *k* affect the comparison;			There is no citation to a comparable step in Subbiah.
(g) establishing crystallographic phase probability distributions from the comparisons for the			There is no citation to a comparable step in Subbiah.

possible crystallographic phases of reflection *k*;			
(h) repeating steps (c) through (g) as *k* is indexed through all of the plurality of reflections;			Subbiah does use a plurality of reflection in the process to increase the resolution of the macromolecule envelope developed by Subbiah.
(i) deriving an updated electron density map using crystallographic phases determined to be most probable from the crystallographic phase probability distributions for each one of the reflections;	This low-resolution envelope (column 4, lines 22-42) for electron density is then improved by the phase thereof being utilized for the construction of new higher resolution, envelopes in an comparative and iterative process for the electron density distribution as being modeled for the macromolecule. This improvement is detailed further in column 19, line 48, through column 21, line 38, wherein the desired resolution is obtained.	See above for column 4, lines 22-42. [The lengthy section of column 19, line 48, through column 21, line 38 is not reproduced. The text is discussed in the argument.]	There is no teaching in Subbiah about crystallographic phase probability distributions to determine the most likely phase for use in an updated electron density map.
(j) repeating steps (d) through (i) to obtain a final set of crystallographic phases with minimum bias from known electron density maps; and	This resolution is the final set of crystallographic determined electron density distribution with the corresponding probable phases and minimum bias compared to the actual		

	macromolecule structure as required in instant claim 1. The errors are also minimized for new envelopes also as a minimum bias as in instant claim 1 as described in column 21, lines 5-16.		
(k) forming a final electron density map using the final set of crystallographic phases.			